

Letters to the Editor

Causes of death in pediatric systemic lupus erythematosus

Sirs,

Pediatric systemic lupus erythematosus (pSLE) remains a severe disease although its prognosis has improved with time. Use of new therapies may result in modifying the causes of mortality. Death was mostly due to renal insufficiency and infections (1-4) during the 1980-1990 decade, while no death was recorded in the sole study enrolling children strictly after 1990 (5). The purpose of this study is to document the changes in causes of mortality in pSLE over the past 10 years in order to better prevent them.

This French retrospective multicenter study included all pSLE patients followed in pediatric centers who died before the age 18 years during the 1996-2006 decade. All of them fulfilled the American College of Rheumatology (ACR) classification criteria for SLE, and were diagnosed before 16 years of age. A questionnaire was sent to the 44 pediatric nephrology and rheumatology units of French university hospitals. The authors classified retrospectively the cause of death as organ involvement resulting from active uncontrollable SLE, thrombosis, therapy-related or infection-related event; the predominant cause was

considered when there was some possible overlapping causes of mortality.

Thirty-nine of the 44 (88%) centers responded to our questionnaire and recorded death in 12 patients, whom main demographic and clinical features are summarized in Table I. Death resulted from SLE organ involvement, including three cases of pancreatitis, thrombosis, infection in 5, 4 and 3 patients respectively. A therapy-related event was assessed in one patient who died during a conditioning regimen before autologous bone marrow transplantation (ABMT), and was suspected in another who had cerebral histoplasmosis, 5 months after being treated sequentially with rituximab (RTX) and cyclophosphamide (Table I). His serum immunoglobulin G level (400 mg/dL) and lymphocyte count ($1.1 \times 10^9/L$) were low at time of death. The twelfth patient committed suicide.

The present series emphasizes that pSLE remains a potentially fatal disease during the pediatric age. Unfortunately, the retrospective design of this multicenter study did not allow us to determine the mortality rates. Deaths were due to SLE exacerbation, thromboses, infections, but also to new therapies related events. The most significant change in survival over time occurred in patients with renal involvement. Renal failure, responsible for most of the

deaths before 1990 (1-5), was not a cause of mortality anymore. Conversely, within the last decade, new therapies proposed to SLE patients, including RTX and ABMT, result in new toxicities. Tolerance of RTX is generally good in the treatment of autoimmune diseases. However, one out of 48 patients reported in the three pSLE studies (6-8) died from severe sepsis after sequential treatment with intravenous cyclophosphamide and RTX (6), as did one patient of the present series. Although the relationship to RTX therapy was unclear in these two patients, these features highlight that the safety of rituximab remains to be clarified. ABMT resulted in death in one patient; now, it must have almost no indication in the treatment of pSLE. Acute pancreatitis was responsible for death in three patients, including a fulminating pancreatitis revealing SLE in our series. Thus, it should be promptly treated with corticosteroid treatment after infectious disease and side effects of treatment have been excluded. (9). It also highlights the need for pneumococcal immunization in SLE patients since one patient died from pneumococcal sepsis. Thrombosis led to death in 2/4 patients who had antiphospholipid (aPL) antibodies, co-existing with other risk factors for thrombosis, including a prolonged air travel and a pneumococcal sepsis respectively in the

Table I. Clinical and demographic details of the 12 pSLE patients included in the study.

Patient	Age at death (y)/ Sex / Ethnicity	Time elapsed from death (months)	Organ involvement before the event which led to death	aPL positivity	Previous therapies	Cause of death
1	16/F/FOC	81	Arthritis, pericarditis, myocarditis* nephritis (class IV)*, pancreatitis, hemophagocytic syndrome*	No	Pred*, MP**, CYC**, plasmapheresis**	SLE pancreatitis
2	11/F/Ca	0.6	Rash*, pancreatitis, thrombocytopenia*	No	Pred*, MP**	SLE pancreatitis
3	11/M/FOC	6	Rash, pancreatitis	Yes	Pred*	Pulmonary thromboembolism during a long-distance air travel
4	15/F/Af	36	Arthritis, pericarditis, thrombocytopenia, nephritis (class IV)*	No	AZA, Pred*, MP*, CYC*, MMF	Myocardial infarction during conditioning regimen for ABMT
5	5/F/Af	8	Rash, arthritis, endocarditis, pancreatitis nephritis (class IV)	No	Pred, AZA, CYC, MMF*, RTX*, MP**, plasmapheresis**	SLE pancreatitis, microangiopathic vasculopathy
6	9/M/As	36	Neurolupus*, rash*, hepatitis*, pancreatitis, nephritis (class I), thrombocytopenia*	No	Pred*, MP**, antimalarials, CYC*	SLE encephalitis (status epilepticus)
7	9/F/Ca	73	Nephritis (class V), arthritis*, rash	No	Pred*, MMF*, RTX*, AZA, MTX,	Pulmonary haemorrhage
8	16/F/Ca	0.2	Nephritis (class IV)*, lupus vasculitis neurolupus*, pancreatitis	No	Pred*, MP*, CYC*, heparin**	Pulmonary thromboembolism (uncontrolled nephrotic syndrome)
9	9/F/Ma	0.4	Nephritis*, thrombocytopenia*, haemolytic anemia*, arthritis*	Yes	Pred*, MP*, heparin**	Pneumococcal sepsis Catastrophic antiphospholipid syndrome
10	14/F/Ca	34	Rash	No	Antimalarials*	Suicide
11	13/F/FOC	42	Nephritis (class IV), rash, pericarditis, enteritis, seizure*	Yes	Pred*, CYC*, MTX, MMF, RTX, MP**, plasmapheresis**	Histoplasmosis encephalitis
12	15/F/FOC	8	Rash, arthritis*, pancreatitis, lupus neurolupus*	Yes	AZA, Pred*, antimalarials	Streptococcal A sepsis

C: Caucasian; Af: African; As: Asian; FOC: French oversea collectivities; CYC: cyclophosphamide; MTX: methotrexate; MMF: mycophenolate mofetil; AZA: azathioprine; RTX: Rituximab; Pred: prednisone; MP: methylprednisolone shots; aPL: antiphospholipid; ABMT: autologous bone marrow transplantation.

* indicates the treatment and involvements already present when the event which led to death occurred.

** indicates the treatment of the event which led to death.

present series. The recent EULAR expert committee recommendation of using low dose aspirin in SLE patients with aPL antibodies, especially when other risk factors for thrombosis coexist (10), must be prospectively evaluated. Deaths still occur during the pediatric age in pSLE patients. Prompt management of SLE pancreatitis and antipneumococcal immunization are warranted in the management of pSLE patients, and ongoing vigilance is needed after treatment with rituximab.

Acknowledgements

We thank all the participating centers: Drs Niaudet (Paris), Bensman (Paris), Baudouin (Paris), Cochat (Lyon), Tsimaratos (Marseille), Decramer (Toulouse), Llanas (Bordeaux), Gouyon (Angers), Nivet (Tours), Guignonis (Limoges), Champion (Angers), Foulard (Lille), de Parscau (Brest), Bérard (Nice), Guyot (Nantes), Palcoux (Clermont-Ferrand), de Lumley (Limoges), Stéphan (Saint Etienne), Couillaut (Dijon), Garnier (Marseille), Pillet (Bordeaux), Lemelle (Nancy), Faye (Paris), Quartier (Paris), Cimaz (Lyon), Plouvier (Besançon), Bourdat-Michel (Grenoble), Pajot (Toulouse), Devauchelle (Brest), Despert (Tours), Pagnier (Grenoble), Pietrement (Reims), Hatchuel (La Martinique), Mazingue (Lille), Fischbach (Strasbourg), Job-Deslandre (Paris), P. Hubert (Paris), E. Azoulay (Paris).

A. KLEIN, MD¹
R. CIMAZ, MD²
P. QUARTIER, MD³
S. DECRAMER, MD⁴
P. NIAUDET, MD⁵
V. BAUDOUIN, MD⁶
A. BELOT, MD²
B. BADER-MEUNIER, MD³

¹Pediatrics Unit, Hôpital Dupuytren, Besançon, France; ²Pediatric Rheumatology Unit, Hôpital Herriot, Lyon, France; ³Pediatric ImmunoHematology and Rheumatology, Hôpital Necker, Assistance Publique-Hôpitaux de Paris, Paris, France; ⁴Pediatric Nephrology Unit, Hôpital Purpan, Toulouse, France; ⁵Pediatric Nephrology Unit, Hôpital Necker, Assistance Publique-Hôpitaux de Paris, Paris, France; ⁶Pediatric Nephrology Unit, Hôpital R. Debré, Assistance Publique-Hôpitaux de Paris, Paris, France.

Address correspondence to: Dr Brigitte Bader-Meunier, Department of Pediatric Immunology, Hematology, Rheumatology, Necker Hospital, Paris, France.
E-mail: brigitte.bader-meunier@nck.aphp.fr

Competing interests: none declared.

References

- ROOD MJ, TEN CATE R, VAN SUILEKOM-SMIT LW *et al.*: Childhood-onset Systemic Lupus Erythematosus: clinical presentation and prognosis in 31 patients. *Scand J Rheumatol* 1999; 28: 222-6.
- LE THI HUANG D, WECHSLER B, PIETTE JC *et al.*: Clinical manifestations and outcome of childhood systemic lupus erythematosus: a retrospective study of 50 cases. *Eur J Intern Med* 1993; 4: 15-22.

- YANG LY, CHEN WP, LIN CY: Lupus nephritis in children--a review of 167 patients. *Pediatrics* 1994; 94: 335-40.
- BAQI N, MOAZAMI S, SINGH A *et al.*: Lupus nephritis in children: a longitudinal study of prognostic factors and therapy. *J Am Soc Nephrol* 1996; 7: 924-9.
- BRUNNER HI, GLADMAN DD, IBNEZ D *et al.*: Difference in disease features between childhood-onset and adult-onset systemic lupus erythematosus. *Arthritis Rheum* 2008; 58: 556-62.
- NWOBI, ABITBOL CL, CHANDAR J, SEETHERUNVONG W, ZILLERUELO G: Rituximab therapy for juvenile-onset systemic lupus erythematosus. *Pediatr Nephrol* 2008; 23: 413-9.
- WILLEMS M, HADDAD E, NIAUDET P *et al.*: Rituximab therapy for childhood-onset systemic lupus erythematosus. *J Pediatr* 2006; 148: 623-7.
- PODOLSKAYA A, STADERMANN M, PILLKINGTON C, MARKX SD, TULLUS K: B-Cell depletion therapy for 19 patients with refractory systemic lupus erythematosus. *Arch Dis Child* 2007 (Epub ahead)
- RICHER O, ULINSKI T, LEMELLE I *et al.*: Abdominal manifestations in childhood-onset systemic lupus erythematosus. *Ann Rheum Dis* 2007; 66: 174-8.
- BERTSIAS G, IOANNIDIS JPA, BOLETIS J, BOMBARDIERI S, CERVERA R, DOSTAL C: EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. *Ann Rheum Dis* 2008; 2: 195-205.